## CLAIMS

What is claimed is:

1. A method of correlating expression of a nucleic acid that encodes a hairpin ribozyme with the appearance or loss of a detectable phenotype which results from the inhibition or expression of a cellular gene not previously known to result in said phenotype, comprising:

a. producing a cloned transduced cell line which expresses at least one reporter gene and at least one ribozyme from a library of hairpin ribozyme-encoding nucleic acids having randomized recognition sequences;

b. detecting a phenotypic difference between
a cloned transduced cell that expresses at least one hairpin ribozyme encoded by said library, and
a cell of the parental cell line that does not express said hairpin ribozyme

c. isolating and sequencing the ribozyme present in said cloned transduced cells.

2. A method according to Claim 1, wherein the hairpin ribozyme-encoding nucleic acid is operably linked to an inducible promoter.

3. A method according to Claim 1, wherein the hairpin ribozyme-encoding nucleic acid is expressed from a viral vector.

4. A method according to Claim 1, wherein cells are transduced with two reporter genes.

5. A method of determining unknown phenotypic effects of a coding nucleic acid of known sequence, comprising the steps of:

a. co-expressing within a same cell a coding nucleic acid of known sequence and also a hairpin ribozyme that cleaves at least one

ribozyme target site present in said coding nucleic acid of known s quence;

b. detecting phenotypic differences between
cells that simultaneously express said coding nucleic acid of known sequence and said hairpin ribozyme that cleaves said at least one target site present in said coding nucleic acid of known sequence, and
cells that express only said coding nucleic acid of known sequence, or cells that express only said hairpin ribozyme that recognizes a target site present in said coding nucleic acid of known sequence.

6. A method according to Claim 5, wherein the hairpin ribozyme-encoding nucleic acid is operably linked to an inducible promoter.

7. A method according to Claim 5, wherein the hairpin ribozyme-encoding nucleic acid is expressed from a viral vector.

8. A method of identifying a nucleic acid whose gene product mediates binding to a selected ligand, comprising:

a. co-expressing within a same cell a nucleic acid whose gene product mediates binding to a selected ligand, at least one member of a library of hairpin ribozyme-encoding nucleic acids having randomized recognition sequences and at least one reporter gene;

b. identifying and cloning a transduced cell that does not bind to said selected ligand, to yield a population of cloned cells that do not bind to said selected ligand;

c. determining the sequence of the recognition sequence of a ribozyme expressed in said cloned transduced cell;

d. making an oligonucleotide consisting of the recognition sequence, including the GUC cleavage site, of a ribozyme of step c;

e. identifying a nucleic acid whose gene product is recognized by the ribozyme of step c using the oligonucleotide of step d as a probe.

9. A method according to Claim 8, further comprising isolating and sequencing said nucleic acid of claim whose gene product is recognized by the ribozyme of step c.

10. A method according to Claim 9, wherein the selected ligand binds to a cell surface receptor.

11. A method according to Claim 10, wherein the ligand is present on a viral particle.

12. A method according to Claim 9, wherein the hairpin ribozyme-encoding nucleic acid is operably linked to an inducible promoter.

13. A method according to Claim 9, wherein the hairpin ribozyme-encoding nucleic acid is expressed from a viral vector.

14. A method according to Claim 9, wherein the selected ligand binds to a molecule that induces a measurable cellular response, wherein the ligand is selected from the group consisting of:

a. hormone receptors
b. receptor for molecules that induce apoptosis, and
c. drug receptors.

15. A method of identifying regulatory gene products and genes that control the expression of a particular selected gene, comprising the steps of:

a. co-expressing in a same cell a selected reporter gene operably linked to the promoter of a selected gene and at least one member of a library of hairpin ribozyme-encoding nucleic acids having randomized recognition sequences, wherein the mRNA encoded by said reporter gene is not recognized or cleaved by a ribozyme expressed in said cell;
b. identifying and cloning a cell wherein the level of expression of the reporter gene is measurably different from that of a cell that

expresses the reporter gene but does not express said at least one member of the library of hairpin ribozyme-encoding nucleic acids;

c. identifying a nucleic acid expressed in the cells cloned in step b whose gene product is recognized by a ribozyme expressed in said cloned cells.

16. A method according to Claim 15, comprising

a. operably linking the promoter of a selected gene to a first reporter gene in a vector

b. transducing a population of cells with a vector of step a;

c. identifying and cloning a transduced cell that contains the vector of step a, to yield a population of cloned cells that contain said vector;

d. transducing cloned cells of step c with vectors that comprise a library of hairpin ribozyme-encoding nucleic acids having randomized recognition sequences, wherein the vectors further comprise at least one reporter gene different from the reporter gene of step a;

e. identifying and cloning a transduced cell that contains the vectors of steps a and d wherein the level of expression of the reporter gene is measurably different from the cells of step c, to yield cloned transduced cells that contain the vectors of steps a and d wherein the level of expression of the reporter gene is measurably different from the cells of step c;

f. isolating the nucleic acid that encodes the ribozyme that is expressed in said cloned transduced cells of step e;

g. determining the sequence of the recognition sequence of the ribozyme of step f;

h. making an oligonucleotide consisting of the recognition sequence, including the GUC cleavage site, of the ribozyme of step h;

i. identifying a nucleic acid whose gene product is recognized by the ribozyme of step g using the oligonucleotide of step h as a probe.

17. A method according to Claim 15, wherein the selected gene is a leptin gene.

18. A method according to Claim 15, wherein the hairpin ribozyme- ncoding nucleic acid is operably linked to an inducible promoter.

19. A method according to Claim 15, wherein the hairpin ribozyme-encoding nucleic acid is expressed from a viral vector.

20. A method of identifying a gene whose gene product confers sensitivity to a selected chemical compound, comprising:

a. transducing a population of parental cells which are sensitive to a selected chemical compound with vectors that comprise a library of hairpin ribozyme-encoding nucleic acids having randomized recognition sequences, and with a nucleic acid that encodes at least one reporter gene;

b. identifying and cloning a transduced cell that is resistant to said selected chemical compound, to yield a population of cloned transduced cells that are resistant to said selected chemical compound;

c. identifying a nucleic acid whose gene product is recognized by a ribozyme expressed by the cloned transduced cells of step b.

21. A method according to claim 20, comprising:

a. transducing a population of parental cells which are sensitive to a selected chemical compound with vectors that comprise a library of hairpin ribozyme-encoding nucleic acids having randomized recognition sequences, and with a nucleic acid that encodes at least one reporter gene;

b. identifying and cloning a transduced cell that is resistant to said selected chemical compound, to yield a population of cloned transduced cells that are resistant to said selected chemical compound;

c. isolating the nucleic acid that encodes the ribozyme that is expressed in the cloned transduced cells of step b;

d. determining the sequence of the r cognition sequence of the ribozyme of step c;

e. making an oligonucleotid consisting of the recognition sequence, including the GUC cleavage site, of the ribozyme of step c;

f. identifying a nucleic acid whose gene product is recognized by the ribozyme of step d using the oligonucleotide of step e as a probe.

22. An *in vitro* method of detecting at least one ribozyme that cleaves a target nucleic acid, comprising the steps of:

a. hybridizing a library of hairpin ribozyme-encoding nucleic acids having randomized recognition sequences *in vitro* to a target nucleic acid under stringent hybridization conditions in a solution that does not permit cleavage, wherein the ribozymes having recognition sequences that are complementary to the specific target nucleic acid hybridize to the recognition site on the target nucleic acid but do not cleave the target nucleic acid;

b. removing ribozymes that do not bind to the target sequence; and

c. collecting one or more ribozymes that bind to the target nucleic acid.

23. A method according to claim 22, wherein the solution that does not permit cleavage lacks magnesium.

24. A method according to claim 22, wherein the solution that does not permit cleavage comprises a magnesium chelator.

25. A method according to claim 22, wherein the target nucleic acid is attached to a solid substrate.

26. A method according to claim 22, wherein bound ribozymes are enabled to cleave the specific target sequence by the addition of magnesium.

27. A method according to claim 22, wherein

step c comprises enabling bound ribozymes to cleave the specific target sequence, wherein cleavage causes the ribozyme to detach from the target nucleic acid.

28. A method according to claim 22, wherein step d comprises generating a ribozyme gene vector library that consists of the target specific ribozymes eluted in step c of claim 22.

29. A method according to claim 22, wherein the target nucleic acid is selected from the group consisting of: an isolated chromosome, an isolated nucleic acid that encodes a desired gene product, a selected isolated nucleic acid fragment; an isolated polycistronic nucleic acid; a cDNA library, and a total messenger RNA fraction of a cell.

30. A method of identifying at least one ribozyme that cleaves RNAs from a first cell line but not from a second cell line, comprising the steps of:

a. incubating the total RNA from a first cell line in the presence of a library of hairpin ribozyme-encoding nucleic acids having randomized recognition sequences, under stringent hybridization conditions, in the presence of a solution that does not permit ribozymes to cleave their target sequence;

b. removing ribozymes that do not bind to RNA molecules in the RNA preparation;

c. collecting ribozymes that bind to RNA molecules in the RNA preparation;

d. incubating, under stringent hybridization conditions, an RNA preparation from a second cell line in the presence of ribozymes collected in step c in the presence of a solution that does not permit ribozymes to cleave their target sequence;

e. removing ribozymes that do not bind to RNA molecules in the RNA preparation from the second cell line;

f. collecting ribozymes that bind to RNA molecules in the RNA preparation from the second cell line.

31. An *in vivo* method of selecting at least one hairpin ribozyme that cleaves a target r cognition site in a target nucleic acid, comprising the steps of:

a. transducing a population of cells with a vector expressing a library of hairpin ribozyme-encoding nucleic acids having randomized recognition sequences, and with a nucleic acid that encodes at least one FACS-sortable reporter gene, under conditions that result in the expression of multiple different ribozymes per cell;

b. selecting and cloning transduced cells that express at least one ribozyme-encoding nucleic acid whose gene product cleaves a target sequence in a selected target nucleic acid;

c. isolating the ribozyme-encoding nucleic acids from the cloned cells of step b;

d. packaging the ribozyme-encoding nucleic acids of step c;

e. transducing a population of cells with the packaged ribozyme-encoding nucleic acids of step d;

f. selecting and cloning transduced cells of step e that express at least one ribozyme-encoding nucleic acid whose gene product cleaves a target sequence; and

g. isolating the ribozyme-encoding nucleic acid from the cloned cells of step f.

32. A method of detecting a ribozyme that compensates for or results in a genetic defect in a transgenic or chimeric animal, comprising the steps of:

a. transducing embryonic target cells, germ cells or totipotent cell lines with a vector expressing a library of nucleic acids that encodes hairpin ribozymes that recognize a selected target nucleic acid, and also with a nucleic acid that encodes a reporter gene;

b. implanting transduced target cells that express the reporter gene in the uterus of a receptive female;

c. screening any resulting transgenic mammals for a selected phenotype that compensates for the genetic defect;

d. isolating ribozyme-encoding nucleic acids from cells of a transgenic mammal of step c.

33. A method according to claim 32, wherein the genetic defect results in a phenotype that is a member of the group consisting of neurological disorders, Alzheimer's disease, Parkinson's disease.

34. A method according to claim 32, wherein the embryonic cells, germ cells or totipotent cell lines are transduced with multiple vectors that encode different ribozymes, and wherein the multiple vectors are isolated in step f are packaged, used to make additional transgenic mammals wherein said additional transgenic animals express only one ribozyme, the additional transgenic mammals are screened for a selected phenotype that compensates for the genetic defect, and the ribozyme-encoding nucleic acid is isolated from cells of a transgenic mammal having said selected phenotype that compensates for the genetic defect.

35. A method of detecting a transduced cell that contains a genetically engineered hairpin ribozyme-encoding nucleic acid, comprising:

transducing a population of cells with vectors that comprise a library of hairpin ribozyme-encoding nucleic acids having randomized recognition sequences, wherein the vectors further comprise at least one reporter gene; and

detecting a cell that expresses at least one reporter gene.

36. A method according to Claim 35, further comprising:
isolating and cloning a cell that expresses at least one reporter gene.

37. A method according to Claim 35, wherein the hairpin ribozyme-encoding nucleic acid is operably linked to an inducible promoter.

38. A kit, comprising a hairpin ribozyme library having randomized recognition sequences packaged in a vector which is suitable for high level

expression in a wide variety of cells, reagents, and detailed instruction for using the kit and interpreting the results.